REMARKS

Applicant respectfully requests reconsideration. Claims 1-5, 8-20, 22, 27-32, 43, 45-57, 63-65, 70-73, 76-80, 83, 84, 88, 89, 94, 95, 97 and 99 are pending in this application. Claims 5, 13, 15, 47-51, 55, 56, 64 and 65 are withdrawn. Claims 45 and 94 are amended to identify the immunostimulatory nucleic acid as a therapeutic agent, and thereby to provide context for the "second therapeutic agent" recited in claim 63. Support for this amendment can be found at least on page 24, lines 6-7. Claim 48 is amended to correct a typographical error. No new matter has been added.

Claims 1-4, 8-12, 14, 16-20, 22, 27-32, 43, 45, 46, 52-54, 57, 63, 70-73, 76-80, 83, 84, 88, 89, 94, 95, 97 and 99 are pending for examination with claim 1 being an independent claim.

Allowable Subject Matter

Applicant acknowledges the allowability of claims 1-4, 8-12, 14, 16-20, 22, 27-32, 43, 45, 53, 57, 70-73, 76-80, 83, 84, 88, 89, 95, 97 and 99.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 63 and 94 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner asserts that claim 63 is indefinite due to the recitation of "second therapeutic" because the identity of the first therapeutic is unclear. Applicant respectfully disagrees. Claim 63 depends from claim 45, which depends from claim 1, which teaches an immunostimulatory nucleic acid comprising the nucleotide sequence of SEQ ID NO:1. The specification teaches that immunostimulatory nucleic acids are therapeutic agents and that they can be combined with other therapeutic agents. For example, page 24 lines 6-7, of the specification states "when used therapeutically, the immunostimulatory nucleic acids can be used as a stand alone or in combination with another therapeutic agent." Thus in claim 63, the first therapeutic agent is the immunostimulatory nucleic acid of claim 1. The meaning of the term and thus the claim are clear to one of ordinary skill in the art. However, in the interest of

expediting prosecution, Applicant has amended, in a non-limiting manner, claim 45 to indicate that the immunostimulatory nucleic acid of claim 1 is a therapeutic agent.

The Examiner asserts that claim 94 is indefinite due to the recitation of "for example." Applicant has amended the claim to delete this language.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph, enablement

The Examiner rejected claims 46, 52, 54 and 94 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner contends that the rejected claims are not enabled because the specification has not shown that the claimed nucleic acids are therapeutically effective in the treatment of cancer. The Examiner contends that due to insufficient guidance in the specification and the unpredictable nature of the art surrounding cancer therapy, undue experimentation would be required to practice the invention. Applicant respectfully disagrees. The rejected claims are methods for stimulating an immune response in a subject by administering the claimed nucleic acids. The Examiner has misconstrued the claims to be methods for treating cancer, and has then improperly imposed upon Applicant a higher burden of proof respecting enablement. The specification demonstrates that the claimed nucleic acids stimulate both in vivo antigen-specific and in vitro antigen non-specific immune responses. The rejected claims relate to the ability of these nucleic acids to stimulate similar immune responses in subjects having or at risk of having infection or cancer. The Examiner has not established why the claimed nucleic acids would not be immunostimulatory in such subjects and thus the Examiner has not met her burden in rejecting these claims.

The enablement requirement is satisfied if one of ordinary skill in the art is able to make and use the claimed invention without undue experimentation, based on the specification and the knowledge in the art at the time of filing. The experimentation required to make and use the claimed invention may be complex, and still not undue, if the art routinely engages in that level of experimentation. As discussed in previous Office Action responses, multiple factors may be considered in analyzing whether an invention is enabled. In re Wands, 858 F.2d 731; 8 USPQ 2d 1400 (Fed. Cir. 1988). Below Applicant presents the Wands factors as they relate to the rejected claims.

Nature of the invention: The invention relates to the identification of immunostimulatory nucleic acids that minimally comprise the defined core 22 nucleotide sequence of SEQ ID NO:1, and the use of these nucleic acids in stimulating immune responses. These nucleic acids are able to stimulate innate, antigen non-specific immune responses as well as adaptive, antigen-specific immune responses.

Breadth of the claims: The rejected claims relate to methods of stimulating an immune response by administering nucleic acids comprising SEQ ID NO:1 to subjects who have or are at risk of developing an infection (claim 46) or who have or are at risk of developing a cancer (claims 52, 54 and 94), optionally in the presence of an antigen.

Level of ordinary skill in the art: One of ordinary skill in the art would be familiar with nucleic acid synthesis, formulation and administration to human or non-human subjects for the purpose of immune response induction.

State of the Art and Predictability in the Art: The Examiner states that immune responses induced by CpG nucleic acids are heterogeneous and therefore unpredictable, and that the state of the art of cancer therapy is similarly unpredictable. Applicant respectfully disagrees. Applicant reiterates that the rejected claims relate to stimulating an immune response in a subject, including but not limited to subjects having or at risk of having an infection or cancer. Having acknowledged that the claimed nucleic acids induce a variety of immune responses *in vitro* and *in vivo*, the Examiner then fails to establish why similar immune response induction profiles would not be observed in subjects at risk of or having an infection or a cancer. The state of the art with respect to such subjects supports Applicant's position that they are able to stimulate immune responses, as evidenced by van Ojik et al. (Ann. Oncol. 2003 13:157) and Speiser et al. (J. Clin. Invest. 2005 115:739-746).

At the time of filing, the art was aware of the immunostimulatory properties of CpG nucleic acids. (See, for example, US 6,194,388 and US 6,207,646, both filed and issued prior to the effective filing date of the instant application, and disclosing the ability of CpG nucleic acids to stimulate immune responses.) The art was therefore familiar with how to make nucleic acids (including those comprising a defined nucleotide sequence) and how to use such nucleic acids to stimulate immune responses *in vitro* or *in vivo*.

The Examiner cites several references to support the position that immune response induced by CpG nucleic acids are heterogeneous and unpredictable. The Examiner cites Wooldridge et al. (Curr Opin Oncol (2003) 15:440-445) and Agrawal et al. (Mol. Med. Today (2000) 6:72-81) for the assertion that "different effects are observed with different CpG ODNs." Wooldridge et al. reviews different classes of CpG nucleic acids, and documents that these classes stimulate immune responses, and are optimal in different scenarios. This reference acknowledges, rather than refutes, the immunostimulatory effect of CpG nucleic acids. Agrawal et al. is an article summarizing antisense oligonucleotide therapy. The reference suggests that in order to reduce non-antisense related activity of antisense oligonucleotide, CpG motifs should be avoided or at least mutated to their methyl forms. (See pg. 78.) This reference also acknowledges, rather than refutes, the immunostimulatory effect of CpG nucleic acids. Applicant notes that the claimed nucleic acids minimally comprise a defined nucleotide sequence having a fixed number (and location) of CpG dinucleotides.

McCluskie et al. (*Vaccine* (2001), 19:2657-2660) is cited for the proposition that "T-rich immunostimulatory nucleic acids do not induce an immune response". Applicant notes that the T-rich nucleic acid molecule that the Examiner is apparently referring to is ODN 1983, which consists of 20 "T" residues. The relevance of this oligonucleotide to the rejected claims which clearly recite a specific 22 nucleotide consensus sequence that is not a poly-T and which is demonstrated to be immunostimulatory is unclear.

Weiner et al. (J. Leuk. Biol. (2000) 68:456-463) is cited for the proposition that "the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood" and "not all CpG ODN are alike and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence". The Examiner's reasons for citing Weiner et al. appear inapplicable to the claimed invention and the instant specification for a number of reasons. First, understanding mechanism is not a prerequisite to patentability. Second, the claimed invention does not relate to *any* CpG ODN, but rather a family of ODN having at least a 22 nucleotide consensus sequence (i.e., SEQ ID NO:1) to which immunostimulatory activity is attributed. And third, the instant Examples show that the claimed nucleic acids stimulate mouse and human immune cells including B and NK cells.

Significantly, Weiner et al. summarizes the immunostimulatory activity of CpG nucleic acids, and therefore actually argues for, rather than against, predictability in the CpG nucleic acid art. The reference teaches that there is a correlation between the *in vitro* and *in vivo* immunostimulatory effects observed with CpG nucleic acids. (See pg. 457, right column, third paragraph.) The reference discloses that CpG ODNs induce cytokines and activate immune cell subpopulations involved in anti-tumor immunity. (See pg. 460, right column, second paragraph.) The reference further discloses that CpG nucleic acids induce an antigen-specific antibody response and protection against subsequent tumor challenge in a murine tumor model. (See pg. 458, right column, last paragraph.) The instantly claimed nucleic acids possess similar immunostimulatory profiles as those described by Weiner et al., including B and NK cell activation, antigen-specific antibody production, and IP-10, IL-10 and IFN-α secretion. The reference further states that "studies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer" and "extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed *in vivo* data fit well with the *in vitro* data outlined above". (See pgs. 456 and 457). This reference supports the position that CpG nucleic acids can induce an immune response *in vivo*.

The Examiner also considers the state of the art of cancer therapy to be unpredictable. As evidence, the Examiner cites several references to support the proposition that tumor types are varied and "do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes." (Ezzell (J NIH Res (1995) 7:46-49, Forni et al. Cancer Res (2000) 60:2571-2575, Peterson et al. Eur J Cancer (2004) 40:837-844, Schuh Toxicol Pathol (2004) 32(Suppl. 1):53-66, Kelland Eur J Cancer (2004) 40:827-836). Applicant points out that the claimed nucleic acids induce antigen-specific as well as antigen non-specific immune responses. Thus, the claimed nucleic acids are expected to stimulate immune responses regardless of the antigen presentation of a tumor.

The Examiner cites Ballas et al. (J. Immunology (2001) 167:4878-4886) for the teaching that "a single CpG ODN cannot be used to treat all cancers and tumors." However, the Examiner acknowledges that Ballas et al. teaches that "CpG motifs can be custom-tailored for each desired immune effect" and that some CpG nucleic acids activate NK cells and are effective

as a sole therapeutic agent at preventing the development of B16 melanoma. The reference demonstrates that mice injected with B16 tumor have increased survival when treated with CpG nucleic acids. (See pg. 4880, left column.) The reference concludes that rejection of the B16 tumor was due to the ability of CpG ODN to augment the killing activity of NK cells. (See pg. 4882, right column.) The claimed invention does not relate to *any* CpG nucleic acids, but rather a family of nucleic acids having at least a 22 nucleotide consensus sequence (i.e., SEQ ID NO:1) to which immunostimulatory activity is attributed. This reference does not suggest that the CpG nucleic acids of the claimed invention would not be effective in inducing an immune response in a subject.

Furthermore, there is no requirement that the claimed nucleic acids stimulate an immune response in all subjects at risk of or having an infection or a cancer. On the contrary, a claim may encompass inoperative embodiments and still meet the enablement requirement. Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984); In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976); In re Cook, 439 F.2d 730, 732, 169 USPQ 298, 300 (CCPA 1971).

The Examiner cites Chatterjee et al. (*Cancer Immunol Immunother.* (1994) 38:75-82) as teaching that "it has been an art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to the bedside) is a quantum leap." The Chatterjee et al. reference is directed to anti-idiotypic antibody therapy and not the use of immunostimulatory nucleic acids for stimulating an immune response in a subject. In addition, CpG nucleic acids have been shown to stimulate immune responses *in vitro* and *in vivo* in human and non-human subjects, consistent with the instantly claimed methods.

The Examiner makes the unsupported statement that "*in vitro* animal model studies have not correlated well with *in vivo* clinical trial results in patients". (See page 4 of the Office Action). The specification however demonstrates immune stimulation of human cells *in vitro* using the claimed nucleic acids. The Examiner has not established why these *in vitro* data do not correlate with the claimed methods.

Bitton et al. (Curr. Opin. Mol. Therap. (2004) 6(1):17-25) is cited for the teaching that therapeutic vaccines have little use in cancer treatment. However, Bitton et al. documents successful vaccines, such as human papillomavirus (HPV)-16 vaccine and hepatitis B virus

(HBV) vaccine. (See pg. 18, left column, third paragraph). The role of immunostimulatory nucleic acids, such as those currently claimed, in cancer vaccines is not contemplated in this review.

Amount of direction provided by the inventor(s): The Examiner asserts that the "specification does not set forth any teaching or guidance to the skilled artisan for practicing the claimed method." Applicant respectfully disagrees. Applicant teaches how to practice the claimed methods, including how to make the nucleic acids, how to formulate, dose and administer the nucleic acids, what type of antigen (and other therapeutic agent) to administer with the nucleic acids, and to whom to administer the nucleic acids. In view of the state of the art at the time of filing relating to CpG nucleic acids, this guidance is sufficient.

Working examples: As acknowledged by the Examiner, the specification provides a number of Examples demonstrating the immunostimulatory properties of the claimed nucleic acids. (See pages 3-4 of Office Action.) The Examples show, *inter alia*, the ability of the claimed nucleic acids to activate B cells *in vitro* as indicated by proliferation (FIGs. 1, 7 and 12) and surface marker activation (FIG. 6), to stimulate secretion of Th1 cytokines such as IFN-alpha, IP-10 and IL-10 by PBMC *in vitro* (FIGs. 2-4, 8-11 and 13), to induce NK lytic activity *in vitro* (FIG. 14), and to stimulate antigen-specific antibody production *in vivo* when administered with an antigen (FIG. 15). Thus the Examples demonstrate that the claimed nucleic acids can stimulate immune responses *in vivo* and *in vitro*, in the presence and absence of antigen, in human and mouse cells.

In response to the Examiner's queries regarding the similarity of CpG 7909 and the claimed nucleic acids, Applicant points the Examiner to the specification which describes that the claimed nucleic acids were identified by screening approximately 165 nucleic acids for those having immune induction profiles that were comparable to or better than CpG 7909. As shown in the Examples, CpG 7909 and CpG 10106 are able to (a) stimulate proliferation and activation of human B cells *in vitro* to similar levels as shown in FIGs. 1 and 6; (b) stimulate secretion of IFN-alpha, IP-10 and IL-10 from human cells to similar levels as shown in FIGs. 2-4 and 8-10; (c) induce TNF alpha from human cells to similarly low levels as shown in FIG. 11; (d) induce IL-12, IL-6 and TNF alpha secretion in mouse splenocytes to similar levels as shown in FIG. 13; (e) induce mouse B cell proliferation to similar levels as shown in FIG. 12; (f) enhance NK lytic

activity in mouse splenocytes to similar levels as shown in FIG. 14; (g) enhance antibody production (and thus titer) against HBsAg in a murine *in vivo* model system as shown in FIG. 15); and (h) induce a Th1 biased immune response as evidenced by similar ratios of IgG1 vs. IgG2 in mice challenged with HBsAg.

As discussed in Weiner et al. (J. Leuk. Biol. 2000 68:456-463), many of these immune responses correlate with *in vivo* immune response induction in cancer murine models. To this end, CpG 7909 has been shown to induce immune responses in human cancer subjects. For example, van Ojik et al. (Ann. Oncol. 2003 13:157) demonstrates induction of an antigen-specific immune response when CpG 7909 is administered with the MAGE-3 cancer antigen, and Speiser et al. (J. Clin. Invest. 2005 115:739-746) demonstrates induction of an antigen-specific immune response when CpG 7909 is administered with the melanoma A cancer antigen.

Notwithstanding these references, however, Applicant refers the Examiner to the attached press release relating to the clinical trials for CpG 7909 together with chemotherapy in the treatment of non-small lung cell cancer.

Quantity of experimentation needed to practice the invention: In view of the teaching of the instant application and the state of the art at the time of filing, the quantity of experimentation required to practice the method of the rejected claims in no greater than that which the art routinely engages in.

In view of the foregoing, the rejected claims can be practiced without undue experimentation and therefore the claims are enabled. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

Maria A. Trevisan
Registration No.: 48,207
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Date: April 15, 2008
x04.15.08

PRESS RELEASE

Press Release

Coley Pharmaceutical Group Announces Pfizer's Discontinuation of Clinical Trials for PF-3512676 Combined with Cytotoxic Chemotherapy in Advanced Non Small Cell Lung Cancer

WELLESLEY, Mass., June 20 /PRNewswire-FirstCall/ -- Coley Pharmaceutical Group, Inc. (Nasdaq: COLY) today announced that its partner Pfizer has discontinued the development program in lung cancer for PF-3512676, an investigational compound, in combination with cytotoxic chemotherapy. This includes two Phase 3 clinical trials and two Phase 2 clinical trials.

A scheduled interim analysis of the Phase 3 clinical trials by an independent Data Safety Monitoring Committee (DSMC) showed that there was no evidence that PF-3512676 produced additional clinical efficacy over that achieved with the standard cytotoxic chemotherapy regimen alone. The DSMC concluded that the risk-benefit profile did not justify continuation of the trials.

"This news is surprising based on the signs of clinical activity observed with PF-3512676 in Coley's Phase II randomized clinical trial and we are disappointed with this setback in the program," said Robert L. Bratzler, Ph.D., President and Chief Executive Officer of Coley Pharmaceutical Group. "We remain focused on advancing our portfolio of TLR Therapeutic candidates for the treatment of cancer, allergy and asthma, lupus and rheumatoid arthritis, and as a vaccine adjuvant, including novel small molecules and RNA- based drugs targeting TLRs7, 8 and 9."

Investor Call

Coley will be hosting a conference call and webcast today, Wednesday, June 20, 2007 at 4:30 p.m. U.S. Eastern Daylight Time with company management to discuss this development.

To access the live audio broadcast or the subsequent archived recording, visit the Investor Center section of the Coley website located at http://www.coleypharma.com. Please log onto Coley's website several minutes prior to the start of the call to ensure adequate time for any software download that may be required. The webcast is also being distributed through the Thomson StreetEvents Network to both institutional and individual investors. Individual investors can listen to the call at http://www.fulldisclosure.com and institutional investors can access the call via http://www.streetevents.com.

Investors may participate in the conference call by dialing either + 1.866.770.7051 in the U.S. or +1.617.213.8064 outside the U.S. and typing in the passcode 87620189. A replay of the call may also be accessed via telephone by dialing +1.888.286.8010 (U.S.) or +1.617.801.6888(international) with the passcode 61166535. The archived webcast and replay of the call will be available through July 4, 2007.

About Coley Pharmaceutical Group

Coley Pharmaceutical Group, Inc. is an international biopharmaceutical company, headquartered in Wellesley, Massachusetts, USA, that discovers and develops TLR Therapeutics(TM), a new class of investigational drug candidates that direct the human immune system to fight cancers, allergy and asthma disorders and to enhance the effectiveness of vaccines. Coley has established a pipeline of TLR Therapeutic product candidates currently advancing through clinical development with partners and has additional product candidates in preclinical development. Coley has product development, research and license agreements with Pfizer, sanofi-aventis, GlaxoSmithKline, Merck, Novartis Vaccines and the United States government. For further information on Coley Pharmaceutical Group please visit http://www.coleypharma.com.

Safe Harbor Statement

Certain statements in this news release concerning Coley's business are considered "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Any or all of the forward-looking statements in this press release may turn out to be wrong. They can be affected by inaccurate assumptions Coley might make or by known or unknown risks and uncertainties, including, but not limited to: the early stage of product development; uncertainties as to the future success of ongoing and planned clinical trials; the risk that results from early stage clinical trials may not be indicative of results in later stage trials; the unproven safety and efficacy of products under development; intellectual property rights and litigation; competitive products; and other risks identified in Coley's filings with the Securities and Exchange Commission including, but not limited to, Coley's Annual Report on Form 10-K for the fiscal year ended December 31, 2006. Consequently, no forward-looking statement can be guaranteed, and actual results may vary materially. Coley undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by applicable law.

SOURCE Coley Pharmaceutical Group

CONTACT: Susan Hager Senior Director, Investor Relations and Corporate Communications Coley Pharmaceutical Group 1-781-431-9019, shager@coleypharma.com or Karen L. Bergman 1-650-575-1509, kbergman@bccpartners.com or Michelle Corral 1-415-794-8662, mcorral@bccpartners.com both of BCC Partners (US) Web site: http://www.coleypharma.com